CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 040223

Trade Name : ACETAMINOPHEN AND CODEINE PHOSPHATE TABLETS USP

Generic Name: Acetaminophen and Codeine Phosphate Tablets USP 300mg/15mg, 300mg/30mg and 300mg/60mg

Sponsor : Duramed Pharmaceuticals, Inc.

Approval Date: November 18, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 040223

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EA/FONSI				
Pharmacology Review(s)				
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Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
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CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 040223

APPROVAL LETTER

ANDA 40-223

NOV 18 1997

Duramed Pharmaceuticals, Inc.
Attention: John R. Rapoza
5040 Lester Road
Cincinnati, OH 45213

Dear Mr. Rapoza:

This is in reference to your abbreviated new drug application dated November 22, 1996, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Acetaminophen and Codeine Phosphate Tablets USP, 300 mg/15 mg, 300 mg/30 mg, and 300 mg/60 mg.

Reference is also made to your amendments dated June 26, 1997, July 11, 1997, August 28, 1997, September 25, 1997, and October 28, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Acetaminophen and Codeine Phosphate Tablets USP, 300 mg/15 mg, 300 mg/30 mg, and 300 mg/60 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Tylenol® with Codeine Tablets, #2, #3, and #4, respectively, of RW Johnson Pharmaceutical Research Institute). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

11-18-97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040223

FINAL PRINTED LABELING

Usual Adult Dosage: See package insert for complete dosing information.

Dispense in a tight, light-resistant container as defined in USP with a child resistant closure.

Store at controlled room temperature 15°-30°C (59°-86°F). Protect from moisture.

Lot No.:

Exp. Date:

DURAmed

NDC 51285-302-05

Acetaminophen and Codeine Phosphate*

Tablets, USP

300 mg/15 mg

Each Tablet Contains:
Acetaminophen, USP ..... 300 mg
Codeine Phosphate, USP ..... 15 mg
***Warning:** May be habit forming.

CAUTION: Federal law prohibits dispensing without prescription.

1000 Tablets

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

DURAMED PHARMACEUTICALS, INC.
CINCINNATI, OH 45213 USA

L00632 Iss. 6/97

0 28176 30205 6

Usual Adult Dosage: See package insert for complete dosing information.

Dispense in a tight, light-resistant container as defined in USP with a child resistant closure.

Store at controlled room temperature 15°-30°C (59°-86°F). Protect from moisture.

Lot No.:

Exp. Date:

DURAmed

NDC 51285-302-04

Acetaminophen and Codeine Phosphate*

Tablets, USP

300 mg/15 mg

Each Tablet Contains:
Acetaminophen, USP ..... 300 mg
Codeine Phosphate, USP ..... 15 mg
***Warning:** May be habit forming.

CAUTION: Federal law prohibits dispensing without prescription.

500 Tablets

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

DURAMED PHARMACEUTICALS, INC.
CINCINNATI, OH 45213 USA

L00631 Iss. 6/97

0 28176 30204 9

Usual Adult Dosage: See package insert for complete dosing information.

Dispense in a tight, light-resistant container as defined in USP with a child resistant closure.

Store at controlled room temperature 15°-30°C (59°-86°F). Protect from moisture.

Lot No.:

Exp. Date:

DURAmed

NDC 51285-302-02

Acetaminophen and Codeine Phosphate*

Tablets, USP

300 mg/15 mg

Each Tablet Contains:
Acetaminophen, USP ..... 300 mg
Codeine Phosphate, USP ..... 15 mg
***Warning:** May be habit forming.

CAUTION: Federal law prohibits dispensing without prescription.

100 Tablets

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

DURAMED PHARMACEUTICALS, INC.
CINCINNATI, OH 45213 USA

L00630 Iss. 6/97

0 28176 30202 5

DURAmed

NDC 51285-304-04

Acetaminophen and Codeine Phosphate*

Tablets, USP

300 mg/60 mg

Each Tablet Contains:
Acetaminophen, USP ..... 300 mg
Codeine Phosphate, USP ..... 60 mg
***Warning:** May be habit forming.

CAUTION: Federal law prohibits dispensing without prescription.

500 Tablets

Usual Adult Dosage: See package insert for complete dosing information.

Dispense in a tight, light-resistant container as defined in USP with a child resistant closure.

Store at controlled room temperature 15°-30°C (59°-86°F). Protect from moisture.

Lot No.:

Exp. Date:

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

DURAMED PHARMACEUTICALS, INC.
CINCINNATI, OH 45213 USA
Iss. 6/97
L00637

0 28176 30404 3

DURAmed

NDC 51285-304-02

Acetaminophen and Codeine Phosphate*

Tablets, USP

300 mg/60 mg

Each Tablet Contains:
Acetaminophen, USP ..... 300 mg
Codeine Phosphate, USP ..... 60 mg
*Warning: May be habit forming.

CAUTION: Federal law prohibits dispensing without prescription.

100 Tablets

Usual Adult Dosage: See package insert for complete dosing information.

Dispense in a tight, light-resistant container as defined in USP with a child resistant closure.

Store at controlled room temperature 15°-30°C (59°-86°F). Protect from moisture.

Lot No.:

Exp. Date:

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

DURAMED PHARMACEUTICALS, INC.
CINCINNATI, OH 45213 USA
Iss. 6/97
L00636

0 28176 30402 9

DURAmed

NDC 51285-304-05

Acetaminophen and Codeine Phosphate*

Tablets, USP

300 mg/60 mg

Each Tablet Contains:
Acetaminophen, USP ..... 300 mg
Codeine Phosphate, USP ..... 60 mg
***Warning:** May be habit forming.

CAUTION: Federal law prohibits dispensing without prescription.

1000 Tablets

Usual Adult Dosage: See package insert for complete dosing information.

Dispense in a tight, light-resistant container as defined in USP with a child resistant closure.

Store at controlled room temperature 15°-30°C (59°-86°F). Protect from moisture.

Lot No.:

Exp. Date:

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

DURAMED PHARMACEUTICALS, INC.
CINCINNATI, OH 45213 USA
Iss. 6/97
L00638

0 28176 30405 0

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

DURAMED PHARMACEUTICALS, INC.
CINCINNATI, OH 45213 USA

L00635 Iss. 6/97

DURAmed

NDC 51285-303-05

Acetaminophen and Codeine Phosphate*

Tablets, USP

300 mg/30 mg

Each Tablet Contains:
Acetaminophen, USP ..... 300 mg
Codeine Phosphate, USP ..... 30 mg
***Warning:** May be habit forming.

CAUTION: Federal law prohibits dispensing without prescription.

1000 Tablets

Usual Adult Dosage: See package insert for complete dosing information.

Dispense in a tight, light-resistant container as defined in USP with a child resistant closure.

Store at controlled room temperature 15°-30°C (59°-86°F). Protect from moisture.

Lot No.:

Exp. Date:

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

DURAMED PHARMACEUTICALS, INC.
CINCINNATI, OH 45213 USA

L00634 Iss. 6/97

DURAmed

NDC 51285-303-04

Acetaminophen and Codeine Phosphate*

Tablets, USP

300 mg/30 mg

Each Tablet Contains:
Acetaminophen, USP ..... 300 mg
Codeine Phosphate, USP ..... 30 mg
***Warning:** May be habit forming.

CAUTION: Federal law prohibits dispensing without prescription.

500 Tablets

Usual Adult Dosage: See package insert for complete dosing information.

Dispense in a tight, light-resistant container as defined in USP with a child resistant closure.

Store at controlled room temperature 15°-30°C (59°-86°F). Protect from moisture.

Lot No.:

Exp. Date:

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

DURAMED PHARMACEUTICALS, INC.
CINCINNATI, OH 45213 USA

L00633 Iss. 6/97

DURAmed

NDC 51285-303-02

Acetaminophen and Codeine Phosphate*

Tablets, USP

Each Tablet Contains:
Acetaminophen, USP ..... 300 mg
Codeine Phosphate, USP ..... 30 mg
***Warning:** May be habit forming.

CAUTION: Federal law prohibits dispensing without prescription.

100 Tablets

Usual Adult Dosage: See package insert for complete dosing information.

Dispense in a tight, light-resistant container as defined in USP with a child resistant closure.

Store at controlled room temperature 15°-30°C (59°-86°F). Protect from moisture.

Lot No.:

Exp. Date:

Acetaminophen and Codeine* Phosphate Tablets, USP

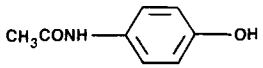
C-III

(*WARNING: May be habit forming)

DESCRIPTION

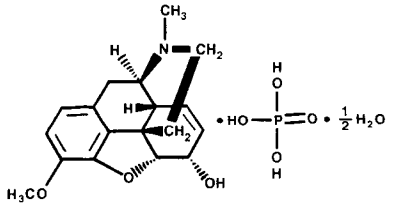
Acetaminophen and codeine is supplied in tablet form for oral administration.

Acetaminophen, 4'-hydroxyacetanilide, a slightly bitter, white, odorless, crystalline powder, is a non-opiate, non-salicylate analgesic and antipyretic. It has the following structural formula:



$C_8H_9NO_2$ MW = 151.17

Codeine phosphate, 7,8-didehydro-4, 5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol phosphate (1:1) (salt) hemihydrate, a white crystalline powder, is a narcotic analgesic and antitussive. It has the following structural formula:



$C_{18}H_{21}NO_3 \cdot H_3PO_4 \cdot {}^1/_2H_2O$ MW = 406.37

Each tablet contains:

Acetaminophen	300 mg
Codeine Phosphate (Warning: May be habit forming)	15 mg
or	
Acetaminophen	300 mg
Codeine Phosphate (Warning: May be habit forming)	30 mg
or	
Acetaminophen	300 mg
Codeine Phosphate (Warning: May be habit forming)	60 mg

In addition, each tablet contains the following inactive ingredients: croscarmellose sodium, microcrystalline cellulose, povidone, pregelatinized starch, silicon dioxide, and stearic acid.

CLINICAL PHARMACOLOGY

This product combines the analgesic effects of a centrally acting analgesic, codeine, with a peripherally acting analgesic, acetaminophen.

Pharmacokinetics: The behavior of the individual components is described below.

Codeine: Codeine is readily absorbed from the gastrointestinal tract. It is rapidly distributed from the intravascular spaces to the various body tissues, with preferential uptake by parenchymatous organs such as the liver, spleen and kidney. Codeine crosses the blood-brain barrier, and is found in fetal tissue and breast milk. The plasma concentration does not correlate with brain concentration or relief of pain; however, codeine is not bound to plasma proteins and does not accumulate in body tissues.

The plasma half-life is about 2.9 hours. The elimination of codeine is primarily via the kidneys, and about 90% of an oral dose is excreted by the kidneys within 24 hours of dosing. The urinary secretion products consist of free and glucuronide conjugated codeine (about 70%), free and conjugated norcodeine (about 10%), free and conjugated morphine (about 10%), normorphine (4%), and hydrocodone (1%). The remainder of the dose is excreted in the feces.

At therapeutic doses, the analgesic effect reaches a peak within 2 hours and persists between 4 and 6 hours.

See OVERDOSAGE for toxicity information.

Acetaminophen: Acetaminophen is rapidly absorbed from the gastrointestinal tract and is distributed throughout most body tissues. The plasma half-life is 1.25 to 3 hours, but may be increased by liver damage and following overdosage. Elimination of acetaminophen is principally by liver metabolism (conjugation) and subsequent renal excretion of metabolites. Approximately 85% of an oral dose appears in the urine within 24 hours of administration, most as the glucuronide conjugate, with small amounts of other conjugates and unchanged drug.

See OVERDOSAGE for toxicity information.

INDICATIONS AND USAGE

Acetaminophen and codeine phosphate tablets are indicated for the relief of mild to moderately severe pain.

CONTRAINDICATIONS

This product should not be administered to patients who have previously exhibited hypersensitivity to codeine or acetaminophen.

WARNINGS

In the presence of head injury or other intracranial lesions, the respiratory depressant effects of codeine and other narcotics may be markedly enhanced as well as their capacity for elevating cerebrospinal fluid pressure. Narcotics also produce other CNS depressant effects, such as drowsiness, that may further obscure the clinical course of the patients with head injuries.

Codeine or other narcotics may obscure signs on which to judge the diagnosis or clinical course of patients with acute abdominal conditions.

Codeine is habit-forming and potentially abusable. Consequently, the extended use of this product is not recommended.

PRECAUTIONS

General: Acetaminophen and codeine phosphate tablets should be prescribed with caution in certain special-risk patients, such as the elderly or debilitated, and those with severe impairment of renal or hepatic function, head injuries, elevated intracranial pressure, acute abdominal conditions, hypothyroidism, urethral stricture, Addison's disease, or prostatic hypertrophy.

Information for Patients: Codeine may impair mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. Such tasks should be avoided while taking this product.

Alcohol and other CNS depressants may produce an additive CNS depression when taken with this combination product, and should be avoided.

Codeine may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Laboratory Tests: In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

Drug Interactions: This drug may enhance the effects of: other narcotic analgesics, alcohol, general anesthetics, tranquilizers such as chlordiazepoxide, sedative-hypnotics, or other CNS depressants, causing increased CNS depression.

Drug/Laboratory Test Interactions: Codeine may increase serum amylase levels.

Acetaminophen may produce false-positive test results for urinary 5-hydroxyindoleacetic acid.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No adequate studies have been conducted in animals to determine whether acetaminophen and codeine have a potential for carcinogenesis or mutagenesis. No adequate studies have been conducted in animals to determine whether acetaminophen has a potential for impairment of fertility.

Acetaminophen and codeine have been found to have no *mutagenic potential* using the Ames Salmonella-Microsomal Activation test, the Basc test on Drosophila germ cells, and the Micronucleus test on mouse bone marrow.

Pregnancy:

Teratogenic Effects: Pregnancy Category C.

Codeine: A study in rats and rabbits reported no teratogenic effect of codeine administered during the period of organogenesis in doses ranging from 5 to 120 mg/kg. In the rat, doses at the 120 mg/kg level, in the toxic range for the adult animal, were associated with an increase in embryo resorption at the time of implantation. In another study a single 100 mg/kg dose of codeine administered to pregnant mice reportedly resulted in delayed ossification in the offspring.

There are no adequate and well-controlled studies in pregnant women. Acetaminophen and codeine phosphate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects:

Dependence has been reported in newborns whose mothers took opiates regularly during pregnancy. Withdrawal signs include irritability, excessive crying, tremors, hyperreflexia, fever, vomiting, and diarrhea. These signs usually appear during the first few days of life.

Labor and Delivery: Narcotic analgesics cross the placental barrier. The closer to delivery and the larger the dose used, the greater the possibility of respiratory depression in the newborn. Narcotic analgesics should be avoided during labor if delivery of a premature infant is anticipated. If the mother has received narcotic analgesics during labor, newborn infants should be observed closely for signs of respiratory depression. Resuscitation may be required (see OVERDOSAGE). The effect of codeine, if any, on the later growth, development, and functional maturation of the child is unknown.

Nursing Mothers: Acetaminophen and codeine are excreted in breast milk in small amounts, but the significance of their effects on nursing infants is not known. Because of the potential for serious adverse reactions in nursing infants from acetaminophen and codeine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

ADVERSE REACTIONS

The most frequently reported adverse reactions are drowsiness, lightheadedness, dizziness, sedation.

shortness of breath, nausea and vomiting. These effects seem to be more prominent in ambulatory than in non-ambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include allergic reactions, euphoria, dysphoria, constipation, abdominal pain, pruritus, rash, thrombocytopenia, agranulocytosis.

At higher doses codeine has most of the disadvantage of morphine including respiratory depression.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: Acetaminophen and Codeine Phosphate tablets are classified as a Schedule III controlled substance.

Abuse and Dependence: Codeine can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychological dependence, physical dependence, and tolerance may develop upon repeated administration and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic medications.

OVERDOSAGE

Following an acute overdosage, toxicity may result from codeine or acetaminophen.

Signs and Symptoms:

Codeine: Toxicity from codeine poisoning includes the opioid triad of: pinpoint pupils, depression of respiration, and loss of consciousness. Convulsions may occur.

Acetaminophen: In acetaminophen overdosage: dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma and thrombocytopenia may also occur.

Early symptoms following a potentially hepatotoxic overdose may include: nausea, vomiting, diaphoresis and general malaise. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

In adults, hepatic toxicity has rarely been reported with acute overdoses of less than 10 grams, or fatalities with less than 15 grams.

Treatment: A single or multiple overdose with acetaminophen and codeine is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended.

Immediate treatment includes support of cardiorespiratory function and measures to reduce drug absorption. Vomiting should be induced mechanically, or with syrup of ipecac, if the patient is alert (adequate pharyngeal and laryngeal reflexes). Oral activated charcoal (1 g/kg) should follow gastric emptying. The first dose should be accompanied by an appropriate cathartic. If repeated doses are used, the cathartic might be included with alternate doses as required. Hypotension is usually hypovolemic and should respond to fluids. Vasopressors and other supportive measures should be employed as indicated. A cuffed endo-tracheal tube should be inserted before gastric lavage of the unconscious patient and, when necessary, to provide assisted respiration.

Meticulous attention should be given to maintaining adequate pulmonary ventilation. In severe cases of intoxication, peritoneal dialysis, or preferably hemodialysis may be considered. If hypoprothrombinemia occurs due to acetaminophen overdose, vitamin K should be administered intravenously.

Naloxone, a narcotic antagonist, can reverse respiratory depression and coma associated with opioid overdose. Naloxone hydrochloride 0.4 mg to 2 mg is given parenterally. Since the duration of action of codeine may exceed that of the nalaxone, the patient should be kept under continuous surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. A narcotic antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

If the dose of acetaminophen may have exceeded 140 mg/kg, acetylcysteine should be administered as early as possible. Serum acetaminophen levels should be obtained, since levels four or more hours following ingestion help predict acetaminophen toxicity. Do not await acetaminophen assay results before initiating treatment. Hepatic enzymes should be obtained initially, and repeated at 24-hour intervals.

Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

Toxic Doses (for adults):

Acetaminophen:	toxic dose 10 g
Codeine:	toxic dose 240 mg

DOSAGE AND ADMINISTRATION

Dosage should be adjusted according to severity of pain and response of the patient.

The usual **adult** dosage is:

	Single Doses (range)	Maximum 24 Hour Dose
Codeine Phosphate	15 mg to 60 mg	360 mg
Acetaminophen	300 mg to 1000 mg	4000 mg

The usual dose of codeine phosphate in **pediatric patients** is 0.5 mg/kg.

Doses may be repeated up to every 4 hours.

The prescriber must determine the number of tablets per dose, and the maximum number of tablets per 24 hours based upon the above dosage guidance. This information should be conveyed in the prescription.

It should be kept in mind, however, that tolerance to codeine can develop with continued use and that the incidence of untoward effects is dose related. Adult doses of codeine higher than 60 mg fail to give commensurate relief of pain but merely prolong analgesia and are associated with an appreciably increased incidence of undesirable side effects. Equivalently high doses in pediatric patients would have similar effects.

HOW SUPPLIED

Acetaminophen and Codeine Phosphate Tablets, USP

300 mg/15 mg tablets: round, white imprinted "H 302" and scored on one side and imprinted "2" on the other side are available in round, white bottles of 100 (NDC 51285-302-02), 500 (NDC 51285-302-04) and 1000 (NDC 51285-302-05) count.

300 mg/30 mg tablets: round, white imprinted "H 303" and scored on one side and imprinted "3" on the other side are available in round, white bottles of 100 (NDC 51285-303-02), 500 (51285-303-04) and 1000 (NDC 51285-303-05) count.

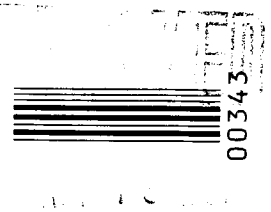
300 mg/60 mg tablets: round, white imprinted "H 304" and scored on one side and imprinted "4" on the other side are available in round, white bottles of 100 (NDC 51285-304-02), 500 (NDC 51285-304-04) and 1000 (NDC 51285-304-05) count.

Dispense in tight, light-resistant container as defined in USP with a child resistant closure.

Store at controlled room temperature, 15°-30°C (59°-86°F). Protect from moisture.

DURAMED PHARMACEUTICALS, INC.
CINCINNATI, OHIO 45213 USA

I00343 Iss. 08/97



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040223

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO. 2

2. ANDA # 40-223

3. NAME AND ADDRESS OF APPLICANT
Duramed Pharmaceuticals, Inc.
5040 Lester Road
Cincinnati, OH 45213

4. LEGAL BASIS FOR SUBMISSION
Certify to the best of their knowledge there are no patents that claim the listed drug product and referenced listed drug is not entitled to a period of marketing exclusivity.
Listed Product: McNeil - Tylenol with Codeine Tablets, #2
McNeil - Tylenol with Codeine Tablets, #3
McNeil - Tylenol with Codeine Tablets, #4

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
None

7. NONPROPRIETARY NAME
Acetaminophen and
Codeine Phosphate

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Firm:
- 11/22/96 - Original.
- 1/22/97 - Response to phone memo.
- 6/26/97 - Facsimile response and O/NC to 1st def. facsimile (chem. & labeling). Subject of this review.
- 7/11/97 - Response to phone memo. Subject of this review.
- 8/28/97 - Response to 2nd def. facsimile (labeling). Subject of this review.
- 9/25/97 - Response to phone memo. Subject of this review.
- 10/28/97 - Response to phone memo. Subject of this review.

FDA:
- 1/13/97 - Phone memo, clarification on GDEA and DMF LOA.
- 1/30/97 - Phone memo, regarding DMF LOA.
- 2/3/97 - Acknowledgment.
- 4/3/97 - Bio. review, acceptable.
- 4/7/97 - Bio. letter, no further questions at this time.
- 4/25/97 - Acceptable MV.
- 6/6/97 - 1st def. facsimile (chem. & labeling).
- 7/10/97 - Phone memo, failed stability samples.
- 8/11/97 - 2nd def. facsimile (labeling).
- 9/22/97 - Phone memo, add *p*-aminophenol to finished product and stability.
- 10/24/97 - Phone memo, add *p*-aminophenol to finished product and stability.

10. PHARMACOLOGICAL CATEGORY
Narcotic Analgesic

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

(b)4 - Confidential Business

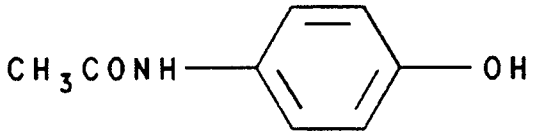
13. DOSAGE FORM
Tablet

14. POTENCY
300 mg/15 mg, 300 mg/30 mg and 300 mg/60 mg

15. CHEMICAL NAME AND STRUCTURE

Acetaminophen USP

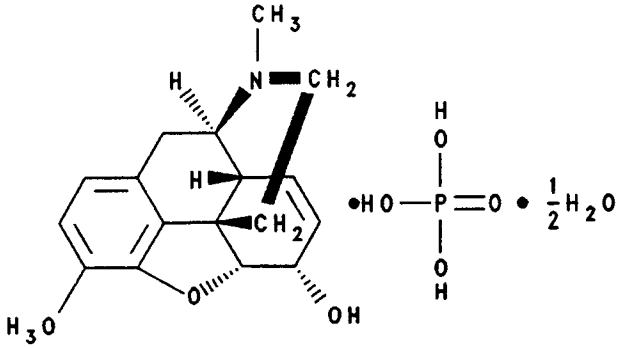
$C_8H_9NO_2$; M.W. = 151.17



4'-Hydroxyacetanilide. CAS [103-90-2]

Codeine Phosphate USP

$C_{18}H_{21}NO_3.H_3PO_4.\frac{1}{2}H_2O$; M.W. = 406.37



7,8-Didehydro-4-5α-epoxy-3-methoxy-17-methylmorphinan-6α-ol phosphate (1:1) (salt) hemihydrate. CAS [41444-62-6]

16. RECORDS AND REPORTS
N/A

17. COMMENTS
Method validation not needed, product is USP. DMFs, labeling, EER, and Bio. are satisfactory

18. CONCLUSIONS AND RECOMMENDATIONS
APPROVAL

19. REVIEWER:
Norman Gregory

DATE COMPLETED:
7/16/97, 9/26/97, 10/30/97 (chem.)
9/5/97 (labeling)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 040223

BIOEQUIVALENCE REVIEW(S)

ANDA 40-223

APR -7 1997

Duramed Pharmaceuticals, Inc.
Attention: John Repoza
5040 Lester Road
Cincinnati, OH 45213

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Acetaminophen and Codeine Phosphate Tablets USP, 300 mg/15 mg, 300 mg/30 mg, 300 mg/60 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.

2. The dissolution testing will need to be incorporated into your stability and quality control programs as specified in USP 23.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Nicholas Fleischer, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

APR - 3 1997

Acetaminophen; Codeine Phosphate
300mg/15mg, 300mg/30mg, 300mg/60mg
Tablets
ANDA #40-223
Reviewer: Z.Z. Wahba
wp# 40223dw.n96

Duramed Pharmaceuticals
Cincinnati, OH
Submission Date:
November 22, 1996

Review of Three Waiver Requests and Dissolution Data

I. BACKGROUND

The firm has submitted comparative dissolution data for its test product, Acetaminophen and Codeine Phosphate Tablets, 300 mg/15 mg, 300 mg/30 mg, 300 mg/60 mg and reference products in support of a request for waiver of in vivo bioequivalence requirements for the test product in accordance with 21 CFR 320.22. The reference listed products is McNeil's Tylenol with Codeine Tablets, 300 mg/15 mg, 300 mg/30 mg, 300 mg/60 mg (ANDA 85-055).

II. FORMULATION COMPOSITION (should not be released under FOI)

Ingredient	300mg/15mg	300mg/30mg	300mg/60mg
	mg/tablet	mg/tablet	mg/tablet
Acetaminophen, USP	300.0	300.0	300.0
Codeine Phosphate, USP	15.0	30.0	60.0
Pregelatinized Starch NF (b)4 -	(b)4 - Confidential Business		
Povidone K-900, USP (b)4 - Confidential			
Stearic Acid, NF			
Microcrystalline Cellulose NF (b)4 -			
Croscarmellose Sodium, NF (b)4 -			
Silicon Dioxide NF			
Purified Water, USP			
Total	400.0	420.0	460.0

* [redacted]/(b)4 - Confidential Business[redacted]

III. DISSOLUTION DATA

The firm has submitted dissolution data for the test and reference products applying the following conditions:

Test product: Hallmark's Acetaminophen and Codeine Phosphate Tablets, 300 mg/15 mg, 300 mg/30 mg, 300 mg/60 mg.

Reference product: McNeil's Tylenol with Codeine Tablets, 300 mg/15 mg, 300 mg/30 mg, 300 mg/60 mg.

Method: USP 23 apparatus II (Paddle) at 50 rpm
Medium: 900 ml 0.1N HCl
Temperature: 37°C ± 0.5°C
Number of Tablets: 12
Time Intervals: 15, 30, 45 and 60 minutes
Specification: NLT [redacted](b)4(Q) is dissolved in 45 minutes

Table 1. In Vitro Dissolution Testing

Drug (Generic Name): Acetaminophen, Codeine Phosphate
Dose Strength: **300 mg/15 mg Tablet**
ANDA No.: 40-223
Firm: Hallmark Pharmaceuticals, Inc.
Submission Date: November 22, 1996
File Name: 40223dw.n96

I. Conditions for Dissolution Testing:

USP XXII Basket: Paddle: X RPM: 50
No. Units Tested: 12
Medium: 0.1N HCl Volume: 900 mL
Specifications: NLT [redacted](b)4(Q) is dissolved in 45 minutes
Reference Drug: McNeil's Tylenol with Codeine Tablets, 300 mg/15 mg
Assay Methodology: [redacted](b)4 -

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Acetaminophen Lot #941204 Strength(mg) 300			Reference Product Acetaminophen Lot # MD5825R Strength(mg) 300		
	Mean %	Range	%CV	Mean %	Range	%CV
15	96.8	[redacted](b)4 -	2.2	100.3	[redacted](b)4 -	1.3

30	98.2	(b)4 - Confidentia Business	1.2	100.5	(b)4 - Confidentia Business	1.1
45	98.3		1.5	100.3		1.2
60	99.0		1.0	100.5		0.7

Sampling Times (Minutes)	Test Product Codeine Lot #941204 Strength(mg) 15			Reference Product Codeine Lot #MD5825R Strength(mg) 15		
	Mean %	Range	%CV	Mean %	Range	%CV
15	99.4	(b)4 - Confidentia Business	1.2	100.9	(b)4 - Confidentia Business	1.1
30	99.8		0.7	100.9		1.2
45	99.7		1.5	100.7		1.2
60	100.1		0.5	101.0		1.2

Table 2. In Vitro Dissolution Testing

Drug (Generic Name): Acetaminophen, Codeine Phosphate
Dose Strength: **300 mg/30 mg Tablet**

Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Acetaminophen Lot #941205 Strength(mg) 300			Reference Product Acetaminophen Lot # MD6223P Strength(mg) 300		
	Mean %	Range	%CV	Mean %	Range	%CV
15	95.8	(b)4 - Confidentia Business	2.4	96.1	(b)4 - Confidentia Business	6.3
30	96.7		2.1	101.1		0.8
45	96.9		1.9	101.2		0.8
60	97.4		1.7	101.4		0.9

Sampling Times (Minutes)	Test Product Codeine Lot #941205 Strength(mg) 30	Reference Product Codeine Lot #ML6223P Strength(mg) 30

	Mean %	Range	%CV	Mean %	Range	%CV
15	98.4	(b)4 - Confidentia Business	2.3	101.8	(b)4 - Confidentia Business	6.1
30	99.8		1.6	102.2		0.9
45	100.1		1.1	102.0		0.9
60	100.6		1.0	101.8		0.9

Table 3. In Vitro Dissolution Testing

Drug (Generic Name): Acetaminophen, Codeine Phosphate
Dose Strength: **300 mg/60 mg Tablet**

Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Test Product Acetaminophen Lot #941206 Strength(mg) 300			Reference Product Acetaminophen Lot # MH5998P Strength(mg) 300		
	Mean %	Range	%CV	Mean %	Range	%CV
15	93.1	(b)4 - Confidentia Business	3.9	50.6	(b)4 - Confidentia Business	16
30	97.8		2.1	101.9		1.0
45	98.5		2.3	101.4		0.6
60	98.7		2.2	102.3		1.1

Sampling Times (Minutes)	Test Product Codeine Lot #941206 Strength(mg) 60			Reference Product Codeine Lot #MH5998P Strength(mg) 60		
	Mean %	Range	%CV	Mean %	Range	%CV
15	94.4	(b)4 - Confidentia Business	4.5	34.8	(b)4 - Confidential Business	27
30	99.4		2.7	101.4		1.2
45	100.3		2.4	101.9		0.9
60	100.8		2.1	102.2		1.0

IV. COMMENTS

1. The drug product is classified "AA" in the list of the "Approved Drug Products with Therapeutic Equivalence Evaluations". The test drug contains active ingredients and dosage forms that are not regarded as presenting either actual or potential bioequivalence problems or drug quality or standards issues.

2. The test drug product contains no inactive ingredient(s) that is known to significantly affect absorption of the active drug ingredient or therapeutic moiety.

3. The dissolution data for the test product is acceptable. The firm followed the dissolution methodology according to the USP 23.

4. The waiver of in vivo bioequivalence study requirements should be granted based on 21 CFR section 320.22(b)(3)(ii) of the Bioavailability/Bioequivalence Regulations.

V. RECOMMENDATION

1. The Division of Bioequivalence agrees that the information submitted by Duramed Pharmaceuticals, Inc. on its drug product, Acetaminophen; Codeine Phosphate Tablets, 300 mg/15 mg, 300 mg/30 mg, 300 mg/60 mg falls under 21 CFR section 320.22(b)(3)(ii) of the Bioavailability/Bioequivalence Regulations. The waiver of in vivo bioequivalence study for the drug is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the firm's test products, Acetaminophen; Codeine Phosphate Tablets, 300 mg/15 mg, 300 mg/30 mg, 300 mg/60 mg are deemed bioequivalent to the currently approved products, McNeil's Tylenol with Codeine Tablets, 300 mg/15 mg, 300 mg/30 mg, 300 mg/60 mg.

2. The dissolution testing conducted by Duramed Pharmaceuticals, Inc. on its drug product, Acetaminophen; Codeine Phosphate Tablets, 300 mg/15 mg, 300 mg/30 mg, 300 mg/60 mg is acceptable.

3. The dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 ml of 0.N HCl at 37°C using Apparatus II (paddle) at 50 rpm. The test product should meet the following specifications:

   Not less than (b)4 of the labeled amount of both

acetaminophen and codeine are dissolved in 45 minutes.

The firm should be informed of the recommendation.

/S/

Zakaria Z. Wahba, Ph.D.
Division of Bioequivalence
Review Branch III

RD INITIALED RMHATRE /S/ 3/28/97
FT INITIALED

Concur: /S/ Date: 4/3/97

for Nicholas Fleisher, Ph.D.
Director
Division of Bioequivalence

cc: ANDA# ~~87-463~~ 40-273, original, HFD-630 (OGD), HFD-604 (Hare), HFD-658 (Mhatre, Wahba), Drug File
ZZWahba/032697/file #40223dw.n96